

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant: Kenneth W. Locke et al.

Examiner: Oh, Taylor V.

Serial No.: 10/601,862

Art Unit: 1625

Filed: June 24, 2003

For: Polymorphic Form A of 4-[6-Acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric Acid

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents

Washington, DC 20231

Sir:

I, Kenneth W. Locke, Ph.D., hereby make the following declaration:

1. I received a Ph.D. degree in Pharmacology from the Emory University School of Medicine in the year 1985.

2. I have 20 years of experience in the pharmaceutical industry focused primarily on drug discovery and the preclinical and early clinical development of novel therapeutics. Each of the positions described below has provided me with the skills, experience and insight to identify promising drug candidates. My career in

the pharmaceutical industry began at Hoechst-Roussel Pharmaceuticals, Inc., heading laboratories for analgesics and anti-inflammatory, and later Alzheimer's disease, drug research. In 1989, I joined Interneuron Pharmaceuticals, Inc., as Manager, Behavioral Neuroscience, taking on positions of increasing responsibility over the next 11 years. Before leaving Interneuron, as Executive Director, Preclinical Development, I was responsible for all aspects of preclinical development for the company's drug portfolio, as well as for in-licensing candidate evaluation. In 2000, I joined Tanabe Research Laboratories U.S.A., Inc., as Vice President of Research, to coordinate the research efforts of chemists and biologists in identifying novel drug development candidates. I am currently employed by MediciNova, Inc., the assignee of the above-referenced patent application, with offices located at 4350 La Jolla Village Drive - Suite 950, San Diego, CA 92122. My current title is Senior Vice President, Portfolio Management.

3. I am named as a co-inventor of the invention claimed in the above-referenced patent application. I have read the contents of the Final Office Action mailed June 5, 2005. I have also been apprised of the Examiner's request, made to assignee's counsel on August 30, 2005, to provide this declaration directed to the superior solubility properties of the claimed orthorhombic crystals of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid (also referred to in the specification of the above-referenced patent application as Form A), as well as the results of certain experiments that are described in Appendix A, attached hereto.

4. As described in the specification of the above-referenced patent application at page 12, Example 5, and also discussed in an amendment dated

February 10, 2005 (at page 5 of the amendment), the claimed orthorhombic crystals (Form A) displayed greater and unexpected solubility compared with the undesired monoclinic crystals of Form B. For example, at 30 °C the solubility of Form B was calculated to be 6.1 g/L, while that of Form A was calculated to be 15.7 g/L – that is, at 30 °C, the claimed orthorhombic crystals displayed more than twice the solubility of the undesired monoclinic crystals. This physical characteristic of greater solubility is also observed at 22 °C and at 40 °C.

5. I would also like to draw the Examiner's attention to Figures 6 and 7 of Appendix A, attached hereto. These figures depict powder x-ray diffraction (PXRD) analyses of tablets made from the claimed orthorhombic crystals and the undesired monoclinic crystals, respectively. As can be readily seen from these figures, the crystalline structure of the two forms, Form A and Form B, are retained in the manufacture of the respective tablets. It is therefore reasonable to assume that the greater solubility characteristics of the claimed orthorhombic crystals are retained in the tablets, which in turn would offer a benefit of greater solubility/bioavailability of active drug to a patient.¹

6. Other aspects of the Appendix A, which are noteworthy, are Figures 2 and 5. Figure 2 depicts the PXRD analyses for the claimed orthorhombic crystals (Form A) versus undesired monoclinic crystals (Form B or Form C). Note, for example, the three singlet peaks for Form A between about 11.5 and 16.0 (2-Theta scale), whereas Forms B and C (both monoclinic) exhibit three doublet peaks in the same region. Figure 5 depicts differential scanning calorimetry (DSC) thermograms

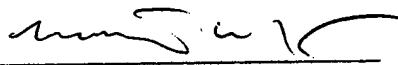
¹ Dissolution experiments using tablets made from different polymorphic forms of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid were inconclusive because tablets were manufactured with widely different particle sizes for the two polymorphic forms. The particle size used for the manufacture of a tablet

of Forms A versus B (including tablets made from the two forms). As can be seen from Figure 5, the phase transition for Form A crystals occurs at a lower temperature than Form B crystals. It may be inferred from these results that Form B is the thermodynamically favored crystal structure for this compound.

7. In summary, the claimed orthorhombic crystals have been shown to exhibit distinct physical and chemical characteristics from the undesired monoclinic forms, including a greater solubility for the claimed orthorhombic crystals relative to undesired monoclinic crystals.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity or enforceability of any patent maturing from the above-referenced patent application.

Dated: Sept. 6, 2005

By: 

Kenneth W. Locke, Ph.D.

